UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,920	09/23/2003	Damian O. Arnaiz	52340AUSM1	3330

27586 7590 05/31/2005

BERLEX BIOSCIENCES
PATENT DEPARTMENT
2600 HILLTOP DRIVE
P.O. BOX 4099
RICHMOND, CA 94804-0099

EXAMINER	
PAVIGLIANITI, ANTHONY JOSEPH	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 05/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,920	ARNAIZ ET AL.	
	Examiner	Art Unit	
	Anthony J. Paviglianiti	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 - 8* is/are pending in the application.

4a) Of the above claim(s) *6 - 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 5* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/03/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date: _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

pD

DETAILED ACTION

Claims 1 – 8 are currently pending in the application. The application was subject to a restriction requirement and Applicant elected **Group I (Claims 1 – 5)**, directed to compounds and compositions. Accordingly, **Claims 6 – 8** were withdrawn from further consideration, pursuant to 37 C.F.R. §1.142(b), as being drawn to a non-elected invention.

Priority

This application claims benefit of U.S. Provisional Application No. 60/413,067, with filing date September 24, 2002.

Information Disclosure Statement

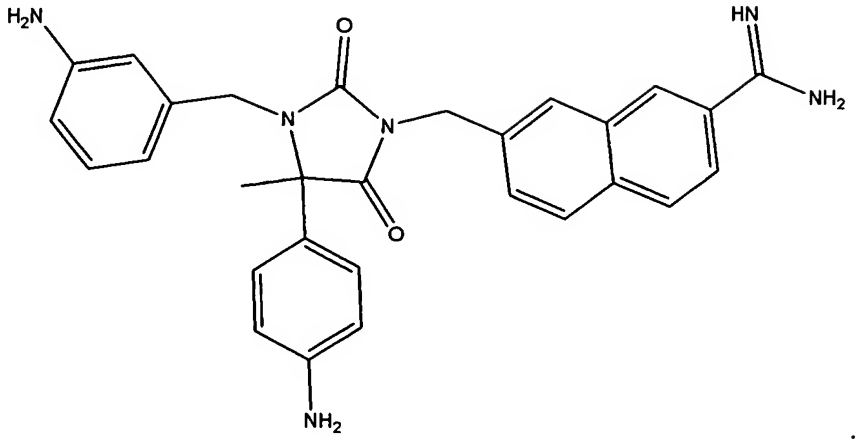
The Information Disclosure Statement filed on March 3, 2004, is in compliance with 37 C.F.R. §1.97 and was considered by the examiner.

Election/Restrictions

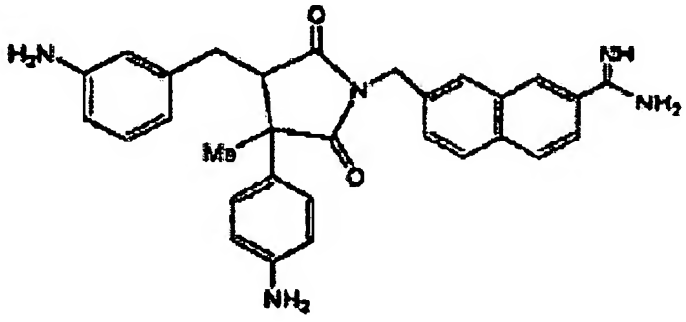
As noted above, the examiner required a restriction in this case, dated November 2, 2004. Applicant's "Response to Restriction Requirement" dated January 26, 2005, is hereby acknowledged.

Applicant's election of "Group I (Claims 1 – 5), subject to the right to rejoin the non-elected method claims of Group II under appropriate conditions," is hereby acknowledged. Applicant has elected the compound **7-[[4-(4-aminophenyl)-3-[(3-aminophenyl)- methyl]-4-methyl-2,5-dioxo-1-imidazolidinyl]methyl]-2-naphthalene carboximidamide, which is "Example 2, compound #49" (Specification at page 24, lines 8 – 13), which has the chemical**

structure:



[Note: The "elected" compound drawn in Applicant's Response to Restriction Requirement

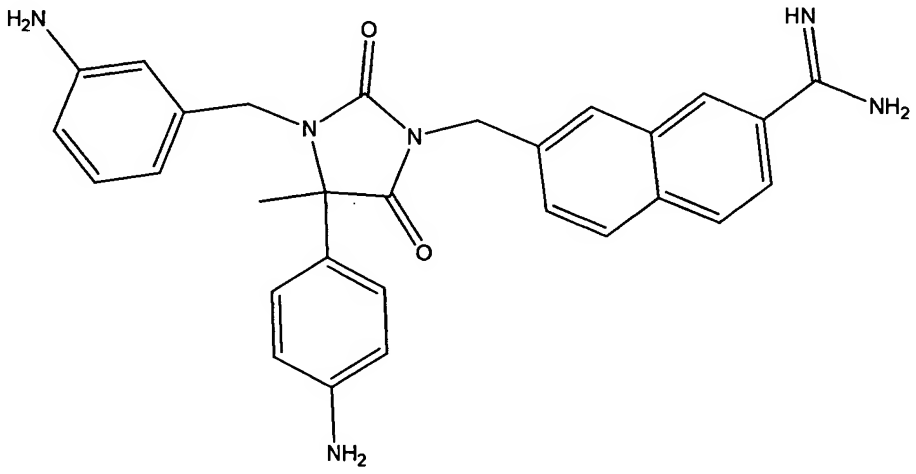


dated January 26, 2005, contains a clerical error, inasmuch as one of the ring nitrogen atoms was inadvertently omitted by Applicant at the 3-position of the heterocyclic ring; and the elected compound, as drawn, would not have been within the scope of the claimed invention, which requires nitrogen atoms at the 1- and 3-position of the five-membered ring. The election of Example 2, compound #49 (Specification at page 24, lines 8 – 13), whereby a nitrogen atom replaced the carbon atom at the 3-position of the five-membered ring, was expressly made and authorized by Melissa Shaw, Esq., by telephone, on May 24, 2005.]

Prior Art Searched

1) The "elected" compound

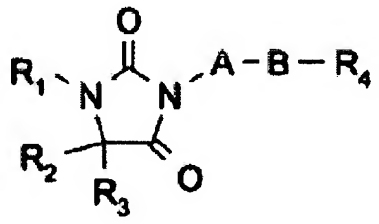
The prior art was searched for the "elected" compound, 7-[[4-(4-aminophenyl)-3-[(3-aminophenyl)methyl]-4-methyl-2,5-dioxo-1-imidazolidinyl]methyl]-2-naphthalene carboximidamide:



However, as described below, prior art was found which anticipated the "elected" compound.

2) Expansion of the search of the prior art beyond the "elected" compound:

Although the "elected" chemical compound was anticipated by a prior art reference, the search of the prior art was broadened beyond the "elected" compound with a series of expanding searches of the art for the following specific limitations for $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, **A**, **B** and $\mathbf{R_4}$ of the genus structure depicted in Claim 1,



:

$\mathbf{R_1}$ is an alkyl, alkenyl, alkynyl, or phenyl group;

$\mathbf{R_2}$ and $\mathbf{R_3}$ are each a hydrogen atom, or an alkyl, alkenyl, alkynyl or phenyl group;

A is a straight chain alkylene, straight chain alkylidene, straight chain alkylidyne, oxo, or sulfonyl group;

B is a phenyl or naphthalenyl group; and

$\mathbf{R_4}$ is an amidine or carboxyamidine group.

The only applicable prior art found during the expansion of searches with the specific claim limitations above was the same reference cited for the "elected" compound, which is described in detail below as the basis for the 35 U.S.C. §102(e)(2) rejection.

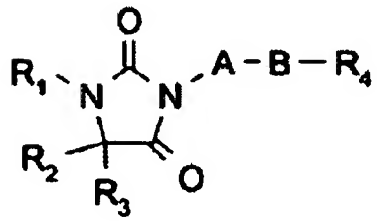
Claim Rejections - 35 USC §102(e)(2)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102(e) that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

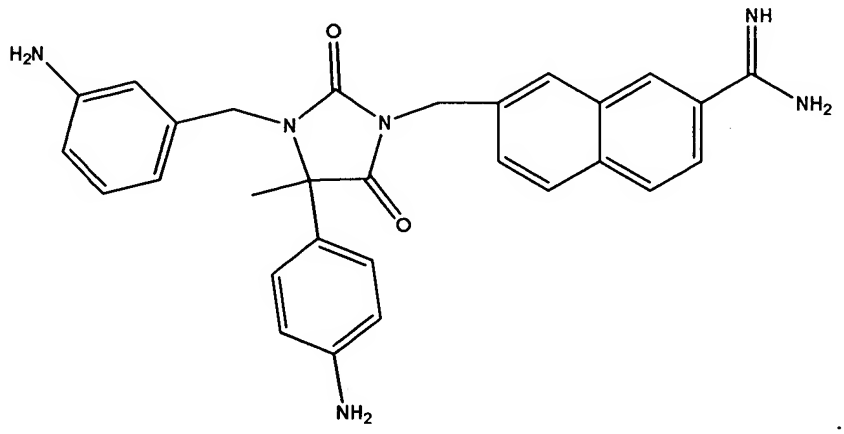
Claim 1 and **Claim 2** are each rejected under 35 U.S.C. §102(e)(2) as being anticipated by **U.S. Patent No. 6,773,896 B2** (issued Aug. 10, 2004; filed May 8, 2002), to Liguo Chi, et al.

The present invention claims compounds of the generic chemical formula:



. Where the generic formula is substituted as follows: $\mathbf{R_1}$ is a 3-amino-methylphenyl group [see note about $\mathbf{R_1}$ in the 112, 2nd paragraph, rejection below]; $\mathbf{R_2}$ is a methyl group; $\mathbf{R_3}$ is a 4-aminophenyl group; **A** is a straight-chain methylene group; **B** is a

naphthalene group; and R_4 is a 2-carboxamidine group, the compound thus formed is anticipated by **U.S. Patent No. 6,773,896 B2**, which disclosed the compound 7-[(R)-3-(3-amino-benzyl)-4-(4-aminophenyl)-4-methyl-2,5-dioxo-imidazolidin-1-ylmethyl]-naphthalene-2-carboxamidine ("PD 313049"), with the structure:



. See U.S. Patent No. 6,773,896 B2, at col. 2, lines 29 – 33. The prior art reference therefore discloses a chemical *species* which anticipated the *genus* chemical structure claimed in the present invention, and therefore supports rejection of **Claim 1** pursuant to 35 U.S.C. §102(e). See MPEP 2131.02 ("A Species Will Anticipate a Claim to a Genus").

In addition to anticipating the genus structure, the same compound in the prior art reference directly anticipates one of the embodiments of the present invention, described as "Example 2, compound #49" (Specification at page 24, lines 8 – 13, prepared as the trifluoroacetate salt), which was the "elected" embodiment of the invention selected by the applicant in response to the examiner's restriction requirement.

Claim 2, which depends from **Claim 1** and adds the limitations of "...B is naphthalenyl and R_4 is amidine," is also rejected under 35 U.S.C. §102(e)(2) as being anticipated by the same compound disclosed in **U.S. Patent No. 6,773,896**, 7-[(R)-3-(3-amino-benzyl)-4-(4-

aminophenyl)-4-methyl-2,5-dioxo-imidazolidin-1-ylmethyl]-naphthalene-2-carboxamidine ("PD 313049") which reads on the additional limitations to substituents **B** and R_4. See U.S. Patent No. 6,773,896 at col. 2, lines 29 – 33. The prior art reference discloses a chemical species which directly anticipates genus structure of the independent claim plus the additional limitations in **Claim 2**, and therefore supports the rejection of **Claim 2** brought under 35 U.S.C. §102(e)(2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a), which forms the basis for all obviousness rejections set forth in this Office action:

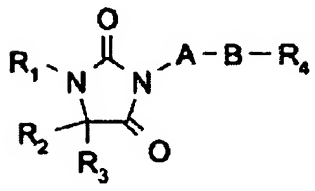
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. §103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over **U.S. Patent No. 6,773,896 B2**, issued to Liguo Chi, et al. (issued August 10, 2004; filed May 8, 2002).

Claim 4, which claims a "pharmaceutical composition" of a compound of the formula



, where the scope of values for R_1, R_2, R_3, **A**, **B** and R_4 are the same as

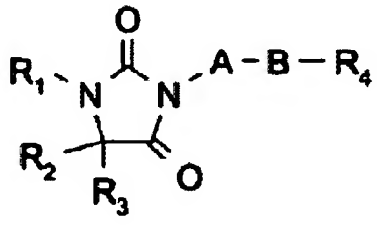
in **Claim 1**, further adds limitations of intended use ("useful in treating a mammal having a disease-state characterized by thrombotic activity..."), is rejected under 35 U.S.C. §103(a) in view of **U.S. Patent No. 6,773,896 B2**. [In this instance, the intended use imparts an additional limitation to the claim which therefore will be examined for patentability. See MPEP 2164.01(c) ("when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation").] **U.S. Patent No. 6,773,896** teaches that the compound 7-[(R)-3-(3-amino-benzyl)-4-(4-aminophenyl)-4-methyl-2,5-dioxo-imidazolidin-1-ylmethyl]-naphthalene-2-carboxamidine ("PD 313049") was administered in two IV bolus doses (0.3 mg/kg or 1.0 mg/kg) to "hypercholesterolemic *rabbits* in a balloon-induced injury model of *thrombosis*" [emphasis added]. See U.S. Patent 6,773,896 at col. 5, lines 14 – 28 and col. 7, lines 21 – 25 and lines 33 - 57. As shown in the analysis below, it would have been obvious to the person of skill in the art to use a "pharmaceutical composition" of the compound "PD 313049" for the intended uses recited in **Claim 4**.

[To state the obvious, rabbits are mammals. See The New Encyclopaedia Britannica, 15th ed. (1994), vol. 23, at page 339 and pages 398 – 401 ("Mammals," entry for order "Lagomorpha (rabbits, hares, pikes)"). Although the activity of compound "PD 313049" was studied for its clotting-factor inhibiting activity by administration to rabbits, U.S. Patent No. 6,773,896 also teaches the application of the assay results to a broader range of animal subjects, including human beings. See, e.g., U.S. Patent No. 6,773,896 at col. 3, lines 6 – 8 ("'Subject' as used herein means all animals including mammals..."). Therefore, this particular limitation of **Claim 4** and **Claim 5** ("in mammals") is directly anticipated by the prior art reference.]

Likewise, **Claim 5** is rejected under 35 U.S.C. §103(a) as being unpatentable over **U.S. Patent No. 6,773,896**, issued to Liguo Chi, et al. (issued August 10, 2004; filed May 8, 2002). **Claim 5**, which is dependent upon **Claim 4**, claims the "pharmaceutical composition" of **Claim 4**, adding further limitations to the intended use to a "disease-state selected from the group consisting of... myocardial infarction...cerebral thromboembolism...pulmonary embolism...deep vein thrombosis," etc. The intended use imparts an additional limitation to the **Claim 5** which therefore will be examined for patentability. See MPEP 2164.01(c) ("when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation"). While the prior art does not expressly teach the use of a composition of "PD 313049" to treat the particular "disease-states" recited in **Claim 5**, it would have been obvious to the skilled artisan that pharmaceutical compositions within the same chemical genus as "PD 313049" would be effective in treating these particular diseases in view of the favorable results taught by U.S. Patent No. 6,773,869.

The Graham factors listed above are applied to **Claim 4** and **Claim 5** as follows:

1. DETERMINING THE SCOPE AND CONTENTS OF THE PRIOR ART

Claim 4 of the present invention claims a "pharmaceutical composition" of a compound of formula 

, along with an intended use ("useful in treating a mammal having a disease-state characterized by thrombotic activity..."). **Claim 5** depends on **Claim 4** and adds limitations to the intended use such that the "disease-state is selected from the

group consisting of unstable angina, myocardial infarction, cerebral thromboembolism, transient ischemic attack, pulmonary embolism," etc.

The prior art reference, **U.S. Patent No. 6,773,896**, teaches that the compound 7-[(R)-3-(3-amino-benzyl)-4-(4-aminophenyl)-4-methyl-2,5-dioxo-imidazolidin-1-ylmethyl]-naphthalene-2-carboxamidine ("PD 313049") was administered in two doses to "hypercholesterolemic rabbits in a balloon-induced injury model of thrombosis" [emphasis added]. See U.S. Patent 6,773,896 at col. 5, lines 14 – 28 and col. 7, lines 21 – 25 and lines 33 - 57. The prior art demonstrates that the compound labeled "PD 313049" decreased Factor VIIa activity, which is involved in clotting activity. Id. at col. 1, lines 21 – 25; and Figure 7, on Sheet 4 of 7.

2. ASCERTAINING THE DIFFERENCES BETWEEN THE PRIOR ART AND THE CLAIMS AT ISSUE

The prior art reference, **U.S. Patent No. 6,773,896**, does not teach administration of the compound labeled "PD 313049" to expressly read on the limitation of "disease-states characterized by thrombotic activity," in **Claim 4**, but only teaches administration of this compound to rabbits in a *balloon-induced injury model of thrombosis*. See Claim 4, page 39, line 14; compare U.S. Patent No. 6,773,896 at col. 5, lines 14 – 28. In the same way, the prior art reference does not expressly teach the administration of a pharmaceutical composition of "PD 313049" for the particular disease-states recited in **Claim 5**, such as myocardial infarction, cerebral thromboembolism, pulmonary embolism, and deep vein thrombosis, but rather shows the compound's inhibitory activity on a clotting factor "FVIIa" at two concentrations.

3. RESOLVING THE LEVEL OF ORDINARY SKILL IN THE PERTINENT ART

However, in light of the teaching of U.S. Patent No. 6,773,896, it would be obvious to a person of skill in the art that, if a particular chemical *species*, 7-[(R)-3-(3-amino-benzyl)-4-(4-

aminophenyl)-4-methyl-2,5-dioxo-imidazolidin-1-ylmethyl]-naphthalene-2-carboxamidine ("PD 313049"), was administered to two hypercholesterolemic rabbits "in a balloon injury model of thrombosis," then pharmaceutical compositions of other compounds within the same chemical *genus* could be administered to treat "disease-states characterized by thrombotic activity" (as in **Claim 4**) with a reasonable expectation of success. See U.S. Patent 6,773,896 at col. 7, lines 21 – 25 and lines 33 – 57; see also Id. at Figure 7 and Figure 8. It would likewise have been obvious to a person of skill in the art that the compositions of the present invention could be used for the specific intended uses recited in the limitations of **Claim 5** (such as myocardial infarction, cerebral thromboembolism, pulmonary embolism, deep vein thrombosis, etc.). Given the favorable results shown in the prior art, the skilled artisan would have been motivated to test other pharmaceutical compositions within the same chemical genus as "PD 313049" for the purpose of "treating disease states characterized by thrombotic activity" (Claim 4) or any of the specific diseases in **Claim 5**, with a reasonable expectation of success.

Therefore, based upon the analysis above, **Claim 4** and **Claim 5** are rejected under 35 U.S.C. §103(a) as obvious over the prior art.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and **Claim 4** are rejected under 35 U.S.C. §112, 2nd paragraph, because each claim defines the variable "$\mathbf{R_1}$" as "...selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, carbocyclic, heterocyclic, heteroaryl and hydrogen." However, the "elected" compound, as well as the majority of the compounds of the invention described in the

Specification (see for instance, the "most preferred compounds of the invention" at p. 11, lines 5 – 24), and all ten individual compounds listed in **Claim 3**, have instead a "benzyl" group (i.e., methylphenyl) substituted at "$\mathbf{R_1}$," which is not within any of the groups recited for "$\mathbf{R_1}$."

This rejection would be obviated by amending Claims 1 and 4 to include the specific group "benzyl" among the values for $\mathbf{R_1}$. This substituent, while not expressly disclosed in the Specification as a value for R_1, has support in the most of the embodiments of the invention. See Specification (pp. 18 – 29) and the original claims (Claim 3, compounds 1 - 10).

Claim 1 and **Claim 4** are also rejected under 35 U.S.C. §112, 2nd paragraph, because each claim recites "...or an *isomer* or *isomeric mixture* thereof..." [emphasis added]. The use of "isomer" and "isomeric mixture" without further limitation of the specific isomer or isomeric mixture of the drawn genus structure renders **Claim 1** and **Claim 4** vague and indefinite, as there is no way for the person of skill in the art to know what particular isomeric arrangement of the atoms is claimed. This is particularly so where the variables cover a wide range of substituents, for instance: "R2 and R3 are each selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, C-amido, carbocyclic, C-carboxy, heteroaryl, heterocyclic and hydrogen. R_2 and R_3 can also be combined to afford a carbocyclic group." (Claim 1, p. 38, lines 8 – 10). The disclosure does not disclose any guidance describing the structure or activity of an isomer or isomeric mixture of the claimed invention.

This rejection would be obviated by deleting the phrase "isomer or isomeric mixture thereof" from Claim 1 and **Claim 4.**

Claim Objections

Claim 3 is objected to as depending upon a rejected base claim (**Claim 1**), but appears to be free of the prior art searched (see "Prior Art Searched" section above) if rewritten in independent form including all of the limitations of the base claim and any intervening claims. See MPEP §608.01(n)(V).

Claim 1 and **Claim 4** are objected to because of the following informalities: the phrase "...combined *to afford* a carbocyclic group" [emphasis added] at p. 38, line 10 and p. 39, line 22, is unclear in this context and should be replaced with "...combined *to form* a carbocyclic group" [emphasis added] for clarity.

Claim 1 and **Claim 4** are also objected to because of the following informalities: "**R2**" and "**R3**" should have the numbers written as subscripts: "$\mathbf{R_2}$" and "$\mathbf{R_3}$," respectively, to be consistent with the drawn structure and the other variables. Appropriate correction is required.

Claim 1 and **Claim 4** are also objected to because each contains a "period" in the middle of the claim. See page 38, line 9 and page 39, line 21. According to MPEP 608.01(m), "Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations." Appropriate correction is required.

Conclusion

Claim 1 and **Claim 2** were rejected under 35 U.S.C. §102(e)(2).

Claim 4 and **Claim 5** were rejected under 35 U.S.C. §103(a).

Claim 1 and **Claim 4** were also rejected under 35 U.S.C. 112, 2nd paragraph.

Claim 3 is objected to as depending upon a rejected base claim but appears to be free of the art of record.

Claim 1 and **Claim 4** are also objected to for claim informalities.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Anthony J. Paviglianiti** whose telephone number is **(571) 272-3107**. The examiner can normally be reached on Monday-Friday, 8:30 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached at (571) 272-0699. **The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Please note that this is a new central FAX number for all official correspondence.**

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anthony J. Paviglianiti
Patent Examiner
TC-1600, Art Unit 1626

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

for Joseph K. McKane
Supervisory Patent Examiner
TC-1600, Art Unit 1626